

treated, the toxicity rate during the early portion of treatment is 1.37%, and that for the out-patient phase of treatment 2.14%—thus giving an estimated total toxicity rate of 3.51%. In Table XI these figures are broken down according to the stage of disease when first treated.

TABLE XI.—Analysis of Rates of Toxic Reactions

	Sero-neg. Primary	Sero-pos. Primary	Secondary	Total
Toxicity rate during hospital phase of treatment	1.41%	1.13%	1.72%	1.37%
Late toxicity rate	1.91%	2.63%	1.54%	2.14%
Overall toxicity rate	3.32%	3.76%	3.26%	3.51%

Summary and Conclusions

An analysis of the results of treatment of 1,028 patients treated for early syphilis, with a schedule consisting of 4,000,000 units of penicillin combined with one course of nearsphenamine and bismuth, is described.

There was a high rate of "default" from surveillance due to the rapid release of patients from the Service. In order to offset this and to obtain a true statistical picture an actuarial method has been used.

If all patients who were considered by the clinician concerned to have become reinfected were accounted for as relapses, then the total cumulative relapse rate at 18 months was found to be 15% and the cumulative muco-cutaneous infectious relapse rate 8.2%. If four of the ten cases clinically diagnosed as reinfections are accepted as such these relapse rates would be 10.8 and 5% respectively. These results would seem to be more satisfactory than those reported by others using commercial penicillin alone and in combination with mapharside by the semi-intensive method.

Treatment failures (cases showing sero-resistance) were small in number, being 0.9% of sero-positive primary cases and 3.87% of secondary cases.

Toxic reactions were of a very low incidence, occurring in 3.51% of all patients treated, and there were no fatalities.

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REFERENCES

- Eagle, H., Magnuson, H. J., and Fleischman, R. (1946). *Vener. Dis. Inform.*, **27**, 3.
 Eames, J. W. (1948). *J. R. Army med. Cps.*, **90**, 282.
 Halley, C. R. L., and Wassermann, H. (1928). *Arch. intern. Med.*, **41**, 843.
 Harrison, L. W. (1945). *Practitioner*, **155**, 223.
 James, C. C. M., Mackay, D. G., and Wright, J. T. (1948). *Brit. J. soc. Med.*, **2**, 18.
 Marshall, J. (1946). *Proc. R. Soc. Med.*, **39**, 465.
 Moore, J. E. (1943). *The Modern Treatment of Early Syphilis*, p. 192. Baillière, Tindall and Cox, London.
 — (1947). *Penicillin in Syphilis*, p. 151. Blackwell, Oxford.
 — (1948). *Brit. J. vener. Dis.*, **24**, 17.
 Reynolds, F. W. (1948). *Vener. Dis. Inform.*, **29**, 272.
 Willcox, R. R. (1946). *J. R. Army med. Cps.*, **87**, 51.

The current issue of the *Practitioner* is devoted to a review of the first year's working of the National Health Service. All the contributors are anonymous, but there is an editorial assurance that they are outstanding in their own spheres. A physician concludes that "there is no evidence that the health of the nation has benefited from the first year of the National Health Service. On the other hand . . . no great harm has resulted." A surgeon puts forward a number of constructive suggestions, and an obstetrician takes the view that "the field is set for a wonderful experiment which could not fail to yield encouraging and possibly dramatic results." General practitioners put forward their own distinctive views, and two newly qualified practitioners contrast their enhanced material security with certain spiritual doubts.

SEX HORMONE UPSET IN AFRICANS

BY

J. N. P. DAVIES, M.D.

Pathologist, Colonial Medical Service, Uganda; Part-time Lecturer in Pathology, Makerere College Medical School

Only in the last few years has interest begun to be focused on the non-parasitic pathology of Africans. The gaps in our knowledge are so immense that it is extremely unwise to be dogmatic on any point in African pathology. Nevertheless, from the few centres where pathological investigations, and particularly necropsies, are being carried out reports are accumulating which show that there are striking differences between the incidence of various lesions in Africans and in Europeans. These have been reviewed by Lewis (1942) and Gelfand (1948). Owing to the total absence of reliable statistics it is usually very difficult to express these differences, and all figures must be interpreted with great caution. Certain of these differences are explicable on climatic or parasitic grounds, others, such as sickle-cell anaemia, on racial grounds, but the majority still defy explanation.

In this paper I suggest that certain of these so far unexplained differences are explicable on the assumption that, because of the almost universal liver damage, Africans are subject to oestrinization on almost a national scale, or even on a continental scale. As chemical analyses of the urines to ascertain sex hormone excretion have not yet been performed, it is proposed to review the evidence supporting this hypothesis.

Malnutrition in Africans

It has long been known that there is a very high incidence of liver disease in Africans and that cirrhosis is extremely common (Vint, 1931); in fact, in East Africans and in the South African Bantu it has been found to be almost universal (Davies, 1948a, b, c; Gillman and Gillman, 1948). Recently evidence has accumulated which suggests that this liver damage is largely the result of malnutrition, assisted perhaps in certain areas by the effects of parasites (Davies, 1948a, b, c). Owing to malnutrition a fatty liver develops early in childhood and cell accumulations then occur with fibrosis, with or without the deposition of iron. Cirrhosis of the liver of a Laennec type often develops even in young children. In those less affected who survive, the liver is permanently marked and often functionally upset.

After childhood is passed recurrent episodes of malnutrition or chronic infections will precipitate further attacks, so that these patients present, both clinically and pathologically, a state somewhat similar to that seen in young children. Other causes of liver damage, such as infectious hepatitis and post-arsenical jaundice, are also common in Africa, and there is reason to suppose that nutritional hepatic necrosis occurs in Africans as it is suspected to do in Ceylon (Fernando, Medonza, and Rajasuriya, 1948). Clinically, Trowell (1946) has found that this malnutritional syndrome, kwashiorkor, is extremely common in African children, and, owing to the prolonged period of breast-feeding and the absence of a proper weaning period, few African children escape without at least a minor attack of the condition. This clinical observation is fully in accord with the pathological finding of almost universal liver damage at necropsy.

There is thus evidence that from early childhood a high proportion of Africans have damaged livers. This has

many profound effects, but in particular it has been shown that when the liver is damaged, as in cirrhosis, it is unable to inactivate oestrogens (Glass, Edmondson, and Soll, 1940). Nor is cirrhosis necessary, for Hibbs (1947) and Klatskin, Salter, and Humm (1947) have described gynaecomastia in malnutrition. It has been shown that the liver fails to inactivate oestrogens where there is vitamin B deficiency (Biskind and Biskind, 1942) or where there is a lack of lipotropic factors (György, 1945). Lipotropic factor deficiency gives rise to fatty infiltration of the liver similar to that found in kwashiorkor (Davies, 1948a, b, c). Therefore, if Africans have damaged livers, which generally is known to be the case, then signs of oestrinization should be widespread in Africa.

Evidence of Oestrinization in Africans

If from an early age Africans are subjected to oestrinization many profound changes might be expected. Most of the experiments performed to show the effect of oestrogens have been carried out in mice and other laboratory animals, and it is as yet uncertain how far similar changes occur in humans. The general change in males is to produce "feminization" associated with certain mental changes. Feminization will be manifested by changes in the general body configuration and by gynaecomastia. The endocrine glands are affected and the incidence of certain endocrine disorders should be altered. The known carcinogenic properties of oestrogens might be expected to be shown by a high incidence of certain types of cancer, and since, if this theory is correct, oestrinization occurs from an early age, then the age incidence of these cancers would probably be lower than in Europeans. In African females a high incidence of cystic hyperplasia of the breast, of endometriosis, and of endometrial cancer might be expected. All these possibilities will be briefly examined.

Changes in the Body Configuration of Africans.—Lewis (1942) points out that the anthropologists have long sought to explain the origin of racial characteristics by the action of hormones and have so explained the slender build of the Bantu (castration effect). Gordon (1933), dealing with amentia in the East African, stated: "I may mention that I have found gynaecomastia to be common and also a marked general feminoid tendency in the males of our own tribes." He also mentioned the frequency of bilateral hyperplasia of the parotids, a condition now known to be associated with malnutrition in Africans (Davies, 1948a; Gillman, Gilbert, and Gillman, 1947). It may be mentioned in passing that the work of Gordon and of Vint (1933) on the African brain and mentality, which attracted great interest, would appear to have been carried out on Africans showing what we now recognize as severe stigmata of malnutrition possibly associated with endocrine upset. In association with this feminization it may be noted that the body and beard hair of Africans is often very soft and downy and they rarely shave, while in health their skins are beautifully soft and satiny.

Gynaecomastia—This is uncommon in temperate regions. Karsner (1946) gives its incidence in the U.S. Army as 16 per 100,000 and in the U.S. Navy as from 6.96 to 9.46 per 100,000. There is no doubt about its frequency in Africans; Gelfand (1948) comments on its prevalence in Rhodesia, and in a recent survey of 500 railway workers in Nairobi Trowell (1948) found it present in moderate degree in 3% of these and in severe degree in 2%. Thus 5% of these supposedly healthy men exhibited this lesion, which Karsner (1946) concluded to be an indication of oestrogen upset in the male. My colleague Mr. E. M. K. Muwazi informs me that in certain parts of

Uganda operations for the removal of these unsightly male breasts are often demanded, and in Mulago Hospital this is an operation not infrequently performed. Testicular atrophy is often associated with gynaecomastia, and while no figures can be given there is no doubt that testicular atrophy and oligospermia are common in Africans.

Inguinal Hernia.—Dr. Burrows has kindly drawn my attention to the effects of oestrogens in causing inguinal hernia to develop in mice. While no figures of exact incidence can be given there is no doubt that hernia is very common in Africans. Connell (1930) has mentioned its frequency in African males and also its relative infrequency in African women. Herniae are extremely common in Uganda and a vast number are operated upon each year. Undescended testicle does not appear to be common, but I am informed (McAdam, 1949—personal communication) that at operation the cord is often found to be short.

Thyrotoxicosis.—The rarity of thyrotoxicosis in Africans is a striking feature of African medicine. While goitre is not uncommon, and is even remarkably common in certain endemic foci—e.g., in Sierra Leone (Blacklock, 1925)—thyrotoxicosis is very rare (Gelfand, 1948). Of the many thousands of biopsy specimens examined in Kampala between 1931 and 1949 only two specimens were found to come from Africans diagnosed as having thyrotoxicosis and with the history supporting this diagnosis. In the same period only one case came to necropsy. Thyroid adenomata, however, are common. Oestrogens are reported as having an inhibitory action on the thyroid (Cameron, 1945), and, though this not so great as to be effective in moderate or severe thyrotoxicosis, in mild cases they may be effective (Farbman, 1944). While the cause of the rarity of thyrotoxicosis in Africans is obscure, it is possible that oestrinization might account for its rarity.

Effects in the Female.—Cystic hyperplasia in women is now attributed to excessive oestrogen stimulation (Willis, 1948). Ellis (1937) refers to the frequency of this condition in African women, finding that in the women he examined 51% had nodules of cystic hyperplasia and 14% had cysts. He thought that, since he found carcinoma of the breast to be unusual in African women, cystic hyperplasia could not be a precancerous lesion. Evidence of the effects of excessive oestrogen stimulation upon the endometrium appears, in my experience, to be frequently seen in the biopsies submitted, but as these are from selected cases no figures can be given. Evidence of infertility is also difficult to produce, but the abortion rate is believed to be high. In their studies in Ulanga, Tanganyika Territory, the Culwicks (1938) found that the fertility rate of the older women was very low, possibly correlated with a severe famine in their youth, but that the fertility rate of the young women, while low, was much higher than that of the older women.

Cancer in Africans

The influence of oestrogens in the causation of cancer has aroused very great interest. The study of the incidence of cancer in Africans is beset with immense difficulties. There is an almost total lack of reliable vital statistics in Central Africa; women come to hospital less often than men, and the severe bed-pressure means that where nothing further can be done patients have to be returned to their homes, while adequate diagnostic facilities are concentrated in a few centres only.

An important consideration is that relatively few Africans live to enter the cancer age, for, as Barnard and Robb-Smith (1945) point out, almost half the total cancer mortality in England and Wales occurs in persons of 65 years and

While the youth of these subjects may be only a reflection of the short life of Africans, these tumours appear predominantly in young males and run an acute course. Another common tumour of Africans which Willis puts in this class of tumours is Kaposi sarcoma, which has a peculiar sex incidence. Elmes and Baldwin record its incidence as 2.4% in their cases. It is possible that some cases of this disease are masquerading in this series under other names—endothelioma or fibrosarcoma.

Primary Liver Carcinoma

This is a very common tumour in Africa, and so far no satisfactory explanation of its frequency has been adduced, but it has been suggested elsewhere that this might also be induced by oestrinization (Davies, 1948b). It has an almost constant association with a slowly developing Laennec type cirrhosis, and Schenken and Burns (1943) have caused hepatomas to develop in mice by oestrogen administration. In Africans it is predominantly a disease of young adult males, the age incidence in this series of 20 necropsy cases being an average of 36.6 years. From such cancerous livers carcinogenic substances have been isolated, probably sterols, as they have from non-cancerous African livers but not from the livers of Europeans or American negroes. Failure of oestrogen inactivation would account for the finding of carcinogens in both cancerous and non-cancerous Bantu livers.

Uterine Carcinoma; Testicular Tumours

Uterine Carcinoma.—Considering the greater ease of diagnosis of cervical cancer as compared with endometrial cancer the incidence of the latter in Uganda would appear to be relatively high. Willis quotes various authorities who suggest that the proportion of cervical to body cancer is about three or four to one.

Testicular Tumours.—These would appear to be rare in Uganda and in Nigeria, and no interstitial-cell tumours are recorded.

Discussion

The evidence which suggests that oestrinization is widespread in Africa and accounts for many of its peculiar pathological conditions requires to be supported by studies of the sex hormone excretion of Africans. To judge by what is known to be true of cirrhotic cases (Lloyd and Williams, 1948), these should present evidence of sex hormone upset. I know of no place in Central Africa where such studies are being carried out, but it would seem that if these were done they might produce extremely interesting results.

If the importance of oestrinization in Africans can be proved it will clearly be a matter of great value in the development of Africa. It is not to be supposed that the evil effects of oestrinization or other hormonal defects induced by malnutrition are confined to the conditions briefly discussed here. Oestrin produces changes in personality and mentality which may be of the greatest importance in African life. While only African pathology has been discussed, the known high incidence of primary hepatic carcinoma in other parts of the world, such as Java and Malaya, may mean that this hypothesis is applicable to conditions there. It is realized that much written here is mere speculative opinion and that other alternative explanations are possible to cover these differences between African and temperate pathology. But all I wish is to lay this hypothesis before those interested in tropical medicine and suggest that the possibility of sex hormone upset in malnourished Africans is a subject worthy of further study.

Summary

It is suggested that the different incidence of a number of pathological states in Africans from that found in Europe can be explained upon the hypothesis that, owing to widespread malnutrition and consequent liver damage, Africans are subject to wholesale oestrinization.

This hypothesis arose out of an investigation into malnutrition carried out in conjunction with Dr. H. C. Trowell and Dr. E. G. Holmes. I am grateful to them, to Dr. A. B. Raper, and to others of my colleagues for help and advice, and also to Dr. H. Burrows. The paper is published with permission of the D.M.S., Uganda.

REFERENCES

- Barnard, W. G., and Robb-Smith, A. H. T. (1945). *Kettle's Pathology of Tumours*. London.
- Biskind, M. S., and Biskind, G. R. (1942). *Endocrinology*, **31**, 109.
- Blacklock, D. B. (1925). *Trans. R. Soc. trop. Med. Hyg.*, **18**, 395.
- Cameron, A. T. (1945). *Recent Advances in Endocrinology*. London.
- Connell, W. K. (1930). *Brit. J. Surg.*, **18**, 16.
- Culwick, A. T., and Culwick, G. M. (1938). *Sociol. Rev.*, **30**, 1.
- Davies, J. N. P. (1947). *E. Afr. med. J.*, **24**, 352.
- (1948a). *Lancet*, **1**, 317.
- (1948b). *Ibid.*, **2**, 474.
- (1948c). *E. Afr. med. J.*, **25**, 117.
- Ellis, M. (1937). *Brit. J. Surg.*, **25**, 39.
- Elmes, B. G. T., and Baldwin, R. B. T. (1947). *Ann. trop. Med. Parasit.*, **41**, 321.
- Farbman, A. A. (1944). Quoted by Cameron (1945).
- Fernando, P. B., Medonza, O. R., and Rajasuriya, P. K. (1948). *Lancet*, **2**, 205.
- Furth, J. (1946). *Physiol. Rev.*, **26**, 47.
- Gelfand, M. (1948). *The Sick African*. Capetown.
- Gillman, J., Gilbert, C., and Gillman, T. (1947). *S. Afr. J. med. Sci.*, **12**, 99.
- and Gillman, T. (1948). *Lancet*, **1**, 169.
- Glass, S. J., Edmondson, H. A., and Soll, S. N. (1940). *Endocrinology*, **27**, 749.
- Gordon, H. L. (1933). *Eugen. Rev.*, **25**, 223.
- Greenstein, J. P. (1947). *Biochemistry of Cancer*. New York.
- György, P. (1945). *Proc. Soc. exp. Biol. N.Y.*, **60**, 344.
- Hennessey, R. S. F. (1942). *E. Afr. med. J.*, **19**, 236.
- Hibbs, R. E. (1947). *Amer. J. med. Sci.*, **213**, 176.
- Karsner, H. (1946). *Amer. J. Path.*, **22**, 235.
- Klatskin, G., Salter, W. T., and Humm, F. D. (1947). *Amer. J. med. Sci.*, **213**, 19.
- Ledentu, G. (1934). *Bull. Soc. Path. exot.*, **27**, 482.
- Lewis, J. H. (1942). *Biology of the Negro*. Chicago.
- Lloyd, C. W., and Williams, R. H. (1948). *Amer. J. Med.*, **4**, 315.
- Schenken, J. R., and Burns, E. L. (1943). *Cancer Res.*, **3**, 693.
- Smith, E. C., and Elmes, B. G. T. (1934). *Ann. trop. Med. Parasit.*, **28**, 461.
- Trowell, H. C. (1946). *E. Afr. med. J.*, **23**, 34.
- (1948). *Ibid.*, **25**, 311.
- Vint, F. W. (1931). *Ibid.*, **7**, 349.
- (1933). *J. Anat.*, **68**, 216.
- (1935). *Lancet*, **11**, 628.
- Willis, R. A. (1948). *Pathology of Tumours*. London.

On the island of Tinian in the trust territory of the Pacific administered by the United States Navy nearly 100 lepers are receiving medical treatment that will enable many of them to return to their former homes and occupations. Work at the leper colony is part of a health service the United States Navy is performing in the Marianas, Caroline, and Marshall Islands. The Navy, acting for the United States Government, directs civil administration in the former Japanese-mandated islands under a trusteeship agreement with the United Nations. A first step in the medical programme was the gathering of information on the health and incidence of disease among the 50,000 natives of the islands. As the 100 inhabited trust islands are scattered over a wide area the U.S.S. *Whidbey*, a small cargo ship fitted as a medical centre, is headquarters for the staff making the survey. The *Whidbey* started making the rounds in the Marshall area in August, 1948. It stops at each inhabited island long enough for a physical and dental examination of every inhabitant. The ship's medical staff consists of two doctors, one dentist, one medical service corps officer, and 10 hospital ratings. One of the most important functions of the staff is to discover cases of leprosy. Although emergency treatment is given on the vessel when necessary, other ships collect the lepers and take them to Tinian Island.